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Prevalence of mental retardation in patients with hereditary retinoblastoma

Annette C. Moll¹
Saskia M. Imhof¹
Elizabeth M. Bleeker-Wagemakers²
Willem Den Otter³
Lex M. Bouter⁴
Jan Willem Koten³
Karel E.W.P. Tan¹

Departments of ¹Ophthalmology and ⁴Epidemiology and Biostatistics,
Free University, Amsterdam; ²Department of Ophthalmogenetics,
The Netherlands Ophthalmic Research Institute, Amsterdam;
³Department of Functional Morphology, Utrecht University, Utrecht,
The Netherlands

Dear Editor,

We evaluated the cumulative incidence of mental retardation in patients with hereditary retinoblastoma. Records of the national Dutch retinoblastoma register were used. This register is complete from 1945 through 1994. Cooperation of the hereditary retinoblastoma patients or their parents was solicited by a letter from the ophthalmologist. The patients with hereditary retinoblastoma born between 1945 and 1970 were visited at home in 1985.¹ On that occasion, information on mental retardation was collected. In addition, questionnaires were sent in 1993 to the patients' parents or caregivers to obtain up-to-date information regarding the patient's condition, visual acuity, and second primary tumors.

Parents of the hereditary retinoblastoma patients born between 1971 and 1994 were visited at home.² Information was obtained on the possible causes of the mental retardation: brain damage or fetal, perinatal, or postnatal disorders (infection, trauma, medication, or anoxia). The reported disorders were verified and the data regarding karyotyping and DNA analyses, if available, were traced by a letter to the general physician. Information regarding the visual acuity, if available, was obtained from the ophthalmic surgeon.

Since the measurement of the intelligence quotient of mentally and visually handicapped persons is complicated and not often valid,³ this parameter cannot be used to define mentally handicapped retinoblastoma patients. Therefore, the following criteria for mental retardation were used: the necessity of residential treatment for mental retardation or home care with day treatment and special education. These criteria only define severely and moderately

Correspondence and reprint requests to:
Willem Den Otter, Ph.D., FUMO, P.O.
Box 80.157, 3508 TD Utrecht, The
Netherlands. Tel: +31-30-2534366 or
+31-33-4940486; Fax: +31-30-2516853

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<i>Bil/uni</i>	<i>Sex</i>	<i>RB</i> (months)	<i>Treatment</i> (OD/OS)	<i>Status</i>	<i>Age</i> (years)	<i>Visus</i>	<i>Chrom/DNA analysis</i>	<i>Midface</i> <i>abnormalities</i>
Bil	F	4	E/E	Alive	50	Blind	Not performed	
Bil	F	21	E/E	Alive	48	Blind	Trisomy 21, no 13q deletion	
Bil	M	3	E/E	Dead	23	Blind	Not performed	
Bil	M	2	E/E	Alive	44	Blind	Not performed	
Bil	M	12	E/X	Dead	7	Impaired	Not performed	
Bil	M	6	E/XLCX	Alive	36	Blind	13q deletion	Yes
Bil	M	10	E/X	Alive	34	Impaired	Not performed	
Bil	M	18	XC/E	Alive	33	Normal	Not performed	
Bil	M	2	E/E	Alive	32	Blind	No chromosomal abnormality	
Bil	F	2	XC/E	Alive	29	Impaired	Not performed	
Bil	F	2	E/XE	Alive	29	Blind	13q14-31 deletion	Yes
Bil	M	24	XE/E	Alive	26	Blind	Not performed	
Bil	M	4	E/E	Alive	26	Blind	Not performed	
Uni	F	8	/E	Alive	24	Normal	13/X translocation	Yes
Bil	F	2	E/X	Alive	21	Impaired	13q14-22 deletion	Yes
Bil	M	6	XCE/E	Alive	19	Blind	XXXXY syndrome, no 13q deletion	Yes
Bil	F	5	E/XE	Alive	19	Blind	Not performed	Yes
Bil	M	2	E/CE	Alive	18	Blind	Not performed	
Bil	M	16	X/X	Alive	13	Impaired	13q13.2-14.2 deletion	Yes
Bil	M	2	X/XE	Dead	3	Impaired	13q13-31 deletion	Yes
Bil	F	11	E/XE	Alive	3	Blind	Trisomy 21, no 13q deletion	

Bil, bilateral; uni, unilateral; RB, age in months at diagnosis retinoblastoma; OD, right eye; OS, left eye; E, enucleation; X, radiation; L, light coagulation; C, chemotherapy; chrom/DNA, chromosomal or DNA analysis; age, age in 1995 or at death.

TABLE 1. Hereditary retinoblastoma patients with mental retardation from the Dutch retinoblastoma register (n=241).

mentally handicapped children. Retinoblastoma was considered as hereditary in cases of bilaterality, family history of retinoblastoma, or a germinal defect in the RB1 gene.

This project was approved by the Medical Ethics Committee of the Free University Hospital, Amsterdam, The Netherlands.

Mental retardation Twenty-one mentally retarded patients were identified among 241 hereditary retinoblastoma patients (8.7%) born in the period 1945-1994 (Table 1). One patient had the unilateral form and a 13/X translocation and was consequently classified as hereditary. It is noteworthy that none of the mentally retarded patients had a positive family history of retinoblastoma.

Results of karyotyping and/or DNA analyses were available for ten of these 21 patients. Chromosomal or DNA analysis was not performed in the 11 'older' cases. All but one of the ten available analyses were abnormal: 13q deletion was found in five patients, trisomy 21 (without 13q deletion) in two, 13/X translocation in one, and a XXXXY-Klinefelter syndrome (without 13q deletion) in one. Only in one case was rubella during pregnancy documented. No other fetal, perinatal, or postnatal problems were recorded. Neither parents nor physicians reported any accident, event, or reason why the patients should have mental retardation. Therefore, it is likely that in most, if

not in all, of the cases mental retardation is related to the observed extensive chromosomal abnormalities that probably also led to retinoblastoma. These abnormalities were not inherited from the parents.

The typical 13q deletion facial appearance described by Motegi et al.⁴ was found in eight of the 21 patients: prominent eyebrows, broad nasal bridge, bulbous tip of the nose, a large mouth with a thin upper lip, and a long philtrum (Table 1). Six of these eight patients had a 13q deletion; no 13q deletion was detectable with karyotyping in one patient and one patient was not tested.

Fifteen patients lived in an institution for visually and mentally handicapped patients, three lived at home with their parents, and three were deceased (14.2%), all due to pneumonia. Two patients had normal vision (9%), six had impaired vision (28%), and 13 were blind (63%) – 12 due to bilateral enucleation. No second primary tumors were found in the 21 mentally retarded retinoblastoma patients.

Discussion and conclusions We stress that we have obtained our results from the complete national register; this excludes ascertainment biases. We found a high cumulative incidence of mental retardation (8.7%) in hereditary retinoblastoma patients. The cumulative incidence of severe and moderate mental retardation in the general population in The Netherlands is about 0.4%.⁵ Thus, the relative risk for mental retardation is about 20 in hereditary retinoblastoma patients. This could even be an underestimation as only the severely and moderately mentally retarded retinoblastoma patients were considered.

The cause of mental retardation in our patient group could not be related to any special event during pregnancy, except for one rubella infection. All other pregnancies and perinatal and postnatal periods were uneventful. We do not consider irradiation therapy to be a cause of mental retardation, as analysis of the data in Table 1 and data on the number of irradiated and non-irradiated patients shows that 7.5% (13 out of 173) of the irradiated patients and 12% (8 out of 68) of the non-irradiated group were mentally retarded. Therefore, it is likely that the association between hereditary retinoblastoma and mental retardation is a specific genetic abnormality.

We did not find any familial mental retardation among the retinoblastoma patients. This was also reported by Tarkkanen.⁶

Our findings confirm those of Motegi et al.⁴ regarding the special appearance of the midface of patients with the 13q deletion. Mostly, these midfacial abnormalities were already detected before irradiation therapy and they were outside the radiation field and different from the late effects of external beam irradiation therapy described by Imhof et al.⁷

In conclusion, one can find patients with retinoblastoma, mental retardation, and midfacial abnormalities (Motegi syndrome). These three phenomena seem to be due to quite extensive chromosomal aberrations. These defects must be new, as none of the eight patients with this triad of abnormalities had a family history of retinoblastoma.

The Motegi syndrome is very rare, although it is frequently found in retinoblastoma patients. This implies that a child with Motegi syndrome must be examined for retinoblastoma.

Sincerely,
Annette C. Mol
Saskia M. Imhof
Elizabeth M. Bleeker-Wagemakers
Willem Den Otter
Lex M. Bouter
Jan Willem Koten
Karel E.W.P. Tan

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